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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,832	03/30/2001	Thomas Tuschl	0399.2008-002	6240

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,832	TUSCHL ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12, 16, 76–78, 81, 86–88, 91, 106, 108, 110, 112, and 115–123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 16, 76–78, 81, 86–88, 91, 106, 108, 110, 112, and 115–123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response, filed 8/14/06, to the Non-Final Office Action of 4/11/06 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 4/11/06 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With the amendment of 8/14/06, claims 12, 16, 76–78, 81, 86–88, 91, 106, 108, 110, 112, and new claims 115–123 are pending and under examination.

Double Patenting

The list of potentially conflicting applications in this case is considered to be extensive. A sampling of such cases follows. This list may not be exhaustive.

Additional applications and issued patents, which may claim the same or similar subject matter include and which are not addressed below include 10/832,248; 10/638,253; and 10/832,432.

If Applicants are aware of any commonly owned pending applications or issued patents, which are not listed below and which claim conflicting subject matter, it is Applicants' duty to

disclose these applications or patents, and to submit an appropriate terminal disclaimer over these applications or patents as pertinent to the instant invention.

Claims 12, 16, 76–78, 81, 86–88, 91, 106, 108 remain provisionally rejected and new claims 115–117 and 119-123 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 7, 8, 13, 14, 20, 25, 27 of copending Application No. 10/255,568. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims isolated RNA of from about 21 to about 23 nucleotides that mediates RNA interference of an mRNA to which it corresponds.

Response to Arguments

Applicants state that, following election, claims 1, 4, 7, 8, 13, 14, 20, and 27 of Application 10/255,568 are withdrawn from consideration. Applicants state that they intend to cancel non-elected claims, for example, claims 1, 4, 7, 8, 13, 14, and 27, in Application No. 10/255,568 in due course. Applicants argue that only claims 20 and 25 of '568 remain relevant to the instant rejection. Applicants assert that the restriction requirements in '568 and the instant application required restriction to products and methods, and that since applicants elected products in the instant case and methods in the '568 case, the instant rejection is inappropriate. Applicants state, however, that they will consider filing a terminal disclaimer should the instant claims be found allowable except for the instant rejection.

Applicants' arguments have been fully considered but are not persuasive.

The instant rejection is maintained because all claims 1, 4, 7, 8, 13, 14, 20, 25, 27 of copending Application No. 10/255,568 are still pending. Though withdrawn, the claims remain active in the case and are eligible for possible rejoinder. Examiners may rejoin claims at any time during prosecution, or be required to rejoin claims at the time of allowance, depending on the claims elected (see MPEP 821.04(b)).

35 USC §121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent.

In the instant case, the conflicting applications are not divisional applications of one another. The applications were not filed as the result of a restriction requirement in one or the other. The applications were voluntarily filed as separate applications. Thus, the prohibition against using the '568 Application as a reference against the instant application does not apply.

Accordingly, the instant rejection is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***

Claims 12, 16, 76, 78, 86, 88, 106, 108, 110, 112, 115-118, and 120-123 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over new claims 30–49 of copending Application No. 11/142,866. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting

application claims a method for chemically and enzymatically synthesizing nuclease resistant (i.e., stabilized) siRNAs of 19-25 nucleotides that mediate RNA interference.

Response to Arguments

Applicants note that Application '866 has not undergone substantive examination. Applicants contend that a provisional obviousness-type double patenting should also be made in the conflicting application, and that the instant rejection, if the only rejection remaining, should be withdrawn to allow the earlier filed application—i.e., the instant case—to issue.

The Examiner acknowledges the requirements with regard to the withdrawal of such provisional rejections. The Examiner notes that conflicting Application '866 is pending following a response to a restriction requirement and that the claims in '866 have been amended, necessitating the revised rejection above.

The instant rejection is therefore maintained for the reasons given above until such time as withdrawal is warranted.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***

Claims 81 and 91 remain rejected and new claims 115-116 (which depend on 81 or 91), and 120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Arguments

Applicants argue that the claimed pharmaceutical compositions have utility in any pharmaceutical (i.e., physiological) application, for example, in cell based applications involving live cells as well as *in vivo* applications, including experimentation and testing in animal models.

Applicants argue that the claimed compositions need only comprise RNAi molecules and a physiologically acceptable carrier.

Applicants argue that the claims do not recite any therapeutic use and the examination of the enablement of such uses is inappropriate.

Applicants further argue that the Examiner has relied upon art documenting the challenges of delivering antisense nucleic acids to cells *in vivo* that is not relevant to RNAi technology. Applicants argue that the references documenting the technical challenges of delivering RNAi molecules to cells *in vivo* are erroneously cited, and that these references instead show that RNAi molecules can be delivered successfully to many cells *in vivo.*

Applicants argue that the Examiner has not met the initial burden of setting forth a reasonable explanation of why the claimed invention is not adequately enabled by the specification, and has therefore not shown sufficient evidence to shift the burden to the applicant.

Applicants argue that undue experimentation does not mean that no experimentation is necessary.

Applicants' arguments have been fully considered but are not persuasive.

The presence of the phrase "pharmaceutical composition" and "pharmaceutically acceptable" in combination with the disclosed *in vivo* uses, including uses in humans (see page 17, lines 15-28, for example; and page 7 beginning at line 24), implies some pharmaceutical use. Therefore, the enablement analysis is based on whether there is any evidence that one skilled in the art could use the composition for any disclosed or well-established pharmaceutical use, i.e., treatment of some disease or condition *in vivo,* without undue experimentation.

Furthermore, the enablement analysis is conducted in view of the state of the art at the time the instant application was effectively filed, 3/30/2000 (MPEP 2164.01). At that time, the use of short interfering RNAs of 21-23 nucleotides to treat disease or modulate gene expression in cells *in vivo* was not well established. Few, if any, documented examples were available. Moreover, the level of skill needed to practice the invention is considered to be high given the well documented challenges of nucleic acid delivery and gene therapy in general, as evidenced by the pre- and post-filing art cited in previous Action. Therefore, in the absence of such prior art guidance, more guidance is necessary to teach one of skill how to deliver compositions comprising dsRNAs to produce a pharmaceutical effect in cells *in vivo.* However, the instant application provides no technical descriptions or representative examples to enable the use of the full scope of the claimed pharmaceutical compositions.

While it may be true that some successful applications of *in vivo* RNAi have been documented in more recent years, many challenges in the field of dsRNA pharmaceuticals remain, and these reports may not be relied upon to show that instant application was enabling as of the earliest filing date. The Examiner has cited several reports in the antisense, ribozyme, and

siRNA fields to show that, overall, the technical challenges inherent in oligonucleotide mediated gene therapy are high. While it may be true that single and double stranded RNAs require different considerations for delivery and uptake, there is sufficient evidence in the post-filing art, examples of which have been cited, to cast doubt on whether the instant application provides enabling support for an invention drawn to pharmaceutical compositions for which the intended use, according to the specification, is to treat disease.

The examiner submits that the extrinsic evidence provided was sufficient to shift the burden to the applicants, and that, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the skilled artisan, at the time the instant application was filed, would have been required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the "pharmaceutical" and "pharmaceutically acceptable" language from the instant claims would overcome this rejection.

***

Claims 110 and 112 remain rejected and new claims 115-123 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to isolated RNA of from about 21 to about 23 nucleotides that mediates RNA interference of a corresponding mRNA, wherein the mRNA is mammalian mRNA, and wherein one or more nucleotides of the isolated RNA are non-naturally occurring nucleotides or deoxyribonucleotides.

Thus, the instant claims encompass DNA/DNA duplexes and fully modified RNA/RNA duplexes, such as fully 2'-O-methyl modified siRNAs for mediating RNA interference. The claims, in fact, encompass any modification, including any 2'-sugar, base, or internucleoside linkage modification and any non-standard nucleotide.

Response to Arguments

Applicants argue that the specification provides sufficient guidance to allow one of skill to make and use the claimed nucleic acids containing one or more non-naturally occurring or non-standard nucleotides. Applicants state that one of skill would know what these non-naturally occurring nucleotides are and how to insert them into a nucleic acid. Applicants state that several published reports confirm the assertions made by applicants that multiple modified nucleotides can be inserted into the claimed RNA and still work in the process of RNA interference. As an example, Applicants cite Chiu and Rana (2003) *RNA* 9:1034-48, as evidence that a number of modified nucleotides can be inserted into RNA without destroying the activity of the molecule.

Applicants further argue that the claims may embrace unoperable species, and that it is not necessary for the claims to specifically exclude inoperable species.

Applicants arguments have been fully considered but are not found persuasive.

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). (MPEP 2164.01 and 2164.05(a))

In the instant case, the Examiner submits that as of 3/30/2000, the earliest effective filing date sought for the instant application, the types of modifications, and the degree of modification that could be made to any given 21-23-nucleotide siRNA was not well known in the prior art. Furthermore, post-filing art clearly shows that, while many modifications do not destroy RNAi activity, several other modifications do, as evidence, for example by Tuschl et al. (US 2004/0259247 A1), and Chiu and Rana (2003) (see Table 1 therein). Further, the rules and generalities, if any, explicitly or implicitly taught by Chiu and Rana, regarding the extent and type of modification that may be incorporated into the sugars, bases, and linkages of any RNAi molecule without destroying RNAi activity were not available to one of skill in the art at the time the instant application was effectively filed.

While the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled, the standard is whether a skilled person could determine

which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling) (MPEP 2164.08(b)).

In the instant case, the Examiner submits that the claims read on significant numbers of inoperative embodiments and the specification does not clearly enable one of skill to distinguish or identify the operative embodiments from the inoperative embodiments without engaging in undue experimentation.

While the specification teaches, for example, that the 3'-overhangs of siRNAs may be modified with 2'-deoxythymidines (page 15), the specification provides no guidance regarding the placement and extent of any other type of modification that may be made to an siRNA without destroying its RNAi activity.

Given that siRNAs fulfill their biochemical function based not only on their complementarity to a target but also on their ability to interact with endogenous proteins and protein complexes, and given that the field of siRNA-mediated RNAi was in its infancy at the time the instant application was effectively filed, it appears that undue, trial and error experimentation would have been required to identify and use the full scope of the chemically modified RNAi-active siRNAs now claimed.

Moreover, with regard to claim 112, written in a product-by-process format, wherein the RNA is obtained by cleavage of dsRNA, it is unclear how fully or even partially 2'-modified or phoshorothioate modified dsRNA may be cleaved or "diced" and, therefore how short dsRNA is

to be produced, since the modifications of this sort are normally intended to stabilize or even prevent nuclease degradation.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims remain and are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 102

Claims 12, 16, 76-78, 81, 86–88, 91, 106, 108, 110, and 112 remain rejected and new claims 115-123 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550).

The claims have been amended to recite isolated RNA of 21 to 23 nucleotides in the form of two separate strands.

Response to Arguments

Applicants argue that Agrawal et al. do not describe a duplex of RNA composed of two separate strands, each strand having a size of 21 to 23 nucleotides.

Applicants' arguments have been fully considered but are not found persuasive. The amendments to the claims fail to overcome the instant rejection for reasons of record and for the reasons that follow.

Specifically, at page 15, beginning at line 31 and continuing to page 16, line 4, Agrawal et al. teach that, in one preferred embodiment, the self-complementary region may be connected to the target hybridizing region by a suitable non-nucleic acid linker. Examples of such linkers include substituted or unsubstituted alkyl groups. In one preferred embodiment the linker is a (ethyleneglycol) 1-6 linker. Agrawal et al. teach that the synthesis may be conveniently carried out by using commercially available triethylene glycol that has a dimethyltrityl protective group at one end and a cyanoethylphosphoramidite group at the other end.

Accordingly, Agrawal et al. explicitly and implicitly disclose self-stabilized oligonucleotides of 8 to 50 nucleotides in length, comprising target hybridizing and self complementary regions (i.e., sense and antisense strands), which may be synthesized independently, as two separate strands, for example, and then tethered or linked together by a non-nucleic acid linker.

Further, as explained previously, Agrawal et al. teach that the target hybridizing and a self complementary regions of the oligonucleotide can be composed of ribonucleotides, deoxyribonucleotides, or both, with ribonucleotide and/or deoxyribonucleotide monomers being connected together via 5' to 3' linkage (pages 8–16, for example). Additionally, it is taught that the oligonucleotide may include modified nucleic acid bases and/or sugars as well as molecules having added substituents, such as diamines, cholesteryl, or other lipophilic groups (pg. 8). In one preferred embodiment, the self-stabilized oligonucleotide is rendered hyperstabilized by

incorporating one or more 2'-O-Me ribonucleotides into the self-complementary region. The target hybridizing region may contain ribonucleotides or 2'-O-Me-ribonucleotides and the self-complementary region may contain DNA" (page 16).

At page 18, top, Agrawal et al. teach that the oligonucleotides of their invention may be used in methods to treat a diseased human or animal in which the disease results from infection with a virus or pathogenic organism, or from the abnormal expression or product of a cellular gene. The method comprises administering self-stabilized oligonucleotides in a pharmaceutically acceptable carrier to the diseased human or animal.

The presence of a 3'-OH group would appear to be an inherent feature of the disclosed oligonucleotides.

Claims 12, 16, 86, 88, 91, and 112 are drafted in the product-by-process format. Even though the reference does not describe the production of the molecule using the methods identical to that recited in the claims, the recitation of a process limitation in the instant claims is not viewed as positively limiting the claimed product absent a showing that the process of making recited in the instant claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and disclosed prior art products.

The method in which the isolated RNAs were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Accordingly, the instant claims remain and are rejected as being anticipated by Agrawal et al.

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Claims 12, 16, 76–78, 81, 86–88, 91, 106, 108, 115–117, and 119-123 are rejected under 35 U.S.C. 102(a) as being anticipated by Hammond et al. (2000) *Nature* 404:293-296, as evidenced by Elbashir et al. (2001) *Genes & Development* 15:188-200.

Hammond et al. teach the production and isolation of short, ~25-nucleotide RNAs from *Drosophila* cell extracts (Figure 4, for example, page 295). It is taught that in plants, the phenomenon of co-suppression has been associated with the existence of small (~25-nucleotide) RNAs that correspond to the gene that is being silenced. Hammond et al. state that "To address the possibility that a similar RNA might exist in *Drosophila* and guide the sequence-specific nuclease in the choice of substrate, we partially purified our activity through several fractionation steps. Crude extracts contained both sequence-specific nuclease activity and abundant, heterogeneous RNAs homologous to the transfected dsRNA (Figs. 2 and 4a)."

Fig. 4 shows an isolated fraction of RNA species, approximately 25 nucleotides in length, derived from the incubation of *cyclin-E* dsRNA with a partially purified *Drosophila* dsRNA nuclease.

Additionally, on page 294, left column, Hammond et al. teach that S2 cells were transfected with dsRNAs corresponding to either *cyclin E* or *lacZ*. Cellular extracts were incubated with synthetic mRNAs of *lacZ* or *cyclin E*. Extracts prepared from cells transfected with the 540-nucleotide *cyclin E* dsRNA efficiently degraded the *cyclin E* transcript; however, the *lacZ* transcript was stable in these lysates (Fig. 2A). Conversely, lysates from cells transfected with the *lacZ* dsRNA degraded the *lacZ* transcript but left the *cyclin E* mRNA intact.

Accordingly, Hammond et al. teach an isolated extract containing short interfering dsRNAs of approximately 25 nucleotides in length generated by a dsRNA-specific nuclease activity in *Drosophila* cells.

Although Hammond et al. do not specifically teach that the the ~25-nucleotide RNA is present in the nuclease complex in a double-stranded or single-stranded form or that it comprises dsRNAs of 21 to 23 nucleotides in length, these species are considered to be inherently disclosed in view of the disclosure of Elbashir et al. (2001) *Genes & Development* 15:188-200.

At page 190, right column, Elbashir et al. provide a detailed analysis of the RNA products formed upon incubation of 39, 52, and 111-bp dsRNAs in *Drosophila* lysate. Elbashir et al. state that dsRNA processing by *Drosophila* cell lysate produces a distribution of different size RNAs, in which 1% are 18-nt, 5%, 19-nt, 12%, 20-nt, 45%, 21-nt, 28%, 22-nt, 6% 23-nt, and 2%, 24-nt.

At page 195, Elbashir et al. propose that the processing of dsRNAs by an RNase III-like enzyme in *Drosophila* cells leads to the production of short RNA duplexes of predominantly 21 and 22-nt in length with staggered 3' ends, 5' phosphates, and 3' hydroxyls.

Accordingly, it is submitted that Hammond et al. teach an isolate comprising a heterogenous population of short interfering, double stranded RNA that includes dsRNAs of 21 to 23 nucleotides in length that have RNAi activity, as evidenced by Elbashir et al. (2001) *Genes & Development* 15:188-200.

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Claims 12, 16, 76–78, 81, 86–88, 91, 106, 108, 110, 112, 115–117, and 119-123 are rejected under 35 U.S.C. 102(a) as being anticipated by Hamilton et al. (1999) *Science* 286:95-952.

Hamilton et al. teach the purification and characterization of a discrete population of ~25-nucleotide RNAs produced in Tomato cells transformed with ACO cDNA sequence, which produces sequence specific gene silencing of the endogenous ACO mRNA (Fig. 1). In fact, Hamilton et al. show the isolation and purification of both a sense and antisense, ~25-nt RNA species corresponding to the ACO sequence (Fig. 1). Similar results were obtained with a GFP transgene, resulting in the production of a population of ~25-nt GFP-specific RNAs (Fig. 3). Again, the short RNAs are isolated inasmuch as they are resolved on a polyacrylamide gel. Hamilton et al. expressly suggest a direct role of the ~25-nt RNAs in post-transcriptional gene silencing (page 951, right column).

Elbashir is relied on for evidence of inherent disclosure for the reasons given above and for those that follow.

Though Hamilton et al. do not specifically teach isolated double stranded, 21 to 23-nucleotide RNAs, isolated RNAs of 21 to 23 nucleotides in length would appear to be inherently decribed given that the ~25-nt RNAs disclosed by Hamilton et al. comprise both sense and antisense, 25-nt RNAs (page 950, middle column and Fig. 1), and given that Elbashir et al. comment on the Hamilton et al. report, stating that "It has been suggested that the 21-23-nt fragments are the guide RNAs for target recognition (Hamilton and Baulcombe 1999)..." (page 188, right column) And "It has been suggested that the 21-23-nt RNA fragments generated by

processing of dsRNAs are the mediators of RNA interference and cosuppression (Hamilton and Baulcombe 1999)..."

Elbashir et al. then go on to show the production of similar size dsRNA fragments by Drosophila cell lysates. It would appear that Elbashir et al. interpret the disclosure by Hamilton and Baulcombe of an isolated species of RNA of "~25-nt" in length to be a population comprising RNAs of sense and antisense orientations ranging from about 21 to about 23-nt in length, consistent with their own findings in Drosophila.

Accordingly, the instant claims are considered to be anticipated by Hamilton et al., as evidenced by Elbashir et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
August 30, 2006